

AR 201-13007A

Alkylphenols Category

Chemical Right-to-Know Initiative

HPV CHALLENGE PROGRAM

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DEVELOPMENT OF ALKYLPHENOL CATEGORY

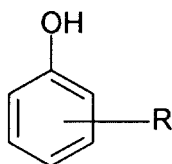
Seventeen alkylphenols listed as High Production Volume (HPV) chemicals are proposed as the members of a chemical category developed using the guidance given in the EPA document, *Development of Chemical Categories in the HPV Challenge Program*.

Originally these phenols were split into four categories using two criteria; position(s) of substituent, *ortho*, *meta*, *para* or a combination of these; and type of substituent, either alkyl or benzyl. However, evaluation of the available physical chemistry, environmental and toxicity data did not, overall, support these categories.

Various alternative classifications were therefore examined. The outcome was the single category now proposed.

Definition of category

Phenol substituted only with one or more alkyl and/or benzyl group(s).



Where R is one or more alkyl and/or benzyl groups

List of Category Members

Name	CAS No.
2,3,6-Trimethylphenol	2416-94-6
<i>p</i> - <i>tert</i> -Butylphenol	98-54-4
<i>o</i> - <i>sec</i> -Butylphenol	89-72-5
2- <i>tert</i> -Butylphenol	88-18-6
<i>p</i> - <i>tert</i> -Amylphenol	80-46-6
Heptyl derivs (<i>p</i> -heptylphenol)	72624-02-3
<i>p</i> - <i>tert</i> -Octylphenol	140-66-9
<i>p</i> -Octylphenol	1806-26-4
2,4-Di- <i>tert</i> -butylphenol	96-76-4
2,6-Di- <i>tert</i> -butylphenol	128-39-2
<i>p</i> -(<i>alpha</i> , <i>alpha</i> -Dimethylbenzyl)phenol	599-64-4

<i>p</i> -Nonylphenol	84852-15-3
2,4-Di- <i>tert</i> -pentylphenol	120-95-6
<i>p</i> -Dodecylphenol	210555-94-5
4- <i>sec</i> -Butyl-2,6-di- <i>tert</i> -butylphenol	17540-75-9
2,4,6-Tri- <i>tert</i> -butylphenol	732-26-3
2,4- Bis(<i>alpha</i> , <i>alpha</i> -dimethylbenzyl)phenol	2772-45-4

Justification for category

Physical chemistry

All the phenols have a single, common functional group; the phenolic hydroxyl. Because alkyl and benzyl groups have a small positive inductive effect all the group phenols are expected to have slightly higher acid dissociation constants (pKa) than phenol (pKa 10.0 at 25°C¹). Data in a review of the physical chemistry properties of substituted phenols² confirms a limited pKa range of 9.9 to 10.9. Therefore none of the category phenols will be ionized significantly at environmental or physiological pH's.

Whilst the category phenols do not, overall, form an homologous series, values for several of the more important physical chemistry parameters do correlate with molecular weight. In particular water solubility and vapor pressure decrease with increasing molecular weight, whilst the octanol/water partition coefficient (log Kow) increases (Table 1).

Environmental distribution and fate

Direct photolysis is not expected to be a significant route of loss for any of the group because of limited absorbance above 290 nm³ but indirect photolysis (atmospheric oxidation) has been estimated for all category members. None of the phenols are expected to be susceptible to abiotic hydrolysis under environmental conditions. Laboratory biodegradation study results were available for under half of the phenols but this information has been supplemented by the inclusion of calculated probabilities (made using the prediction program BIOWIN v3.65) for the remainder. In general the laboratory test data showed, as expected, that the lower molecular weight phenols with simple straight chain substituents were more biodegradable than those with higher molecular weights and more branching.

The level I fugacity modelling shows that, in general, phenols will be located primarily in the soil compartment but that lower molecular weight phenols, with correspondingly higher water solubilities and vapor pressures, will also be present in significant quantities in the air and water compartments (Table 2).

¹ The Merck Index, 11th Edition, p. 1150, Merck & Co., Inc., Rahway, N.J.

² Mackay, D., Varhannickova, D., Ma, Kuo-Ching & Shiu, Wan-Ying, *Chlorophenols and Alkylphenols: A Review and Correlation of Environmentally Relevant Properties and Fate in an Evaluative Environment*, Chemosphere, Vol 29, No. 6, pp 1155-1224, 1994

³ For example *p*-methylphenol, a typical alkylphenol, has molar absorptivities of 18 l/mol-cm at 297.5 nm and only 1 l/mol-cm at 312.5 nm (Smith, J.H. et al, *Environmental Pathways of Selected Chemicals in Freshwater Systems: Part II. Laboratory Studies*, EPA-600/7-78-074, May 1978. Cited in Lyman, W.J., Reehl, W.F. and Rosenblatt, D.H., *Handbook of Chemical Property Calculation Methods*, McGraw-Hill, Inc., Washington, 1990, page 8-38).

Aquatic toxicity

The aquatic toxicity of phenols has been extensively investigated. Using the classification method of Verhaar⁴ all the category phenols would be classified as Type 2 compounds (polar narcotics). Narcosis is a non-specific mode of toxic action caused by disruption of the cell membrane. The ability to induce narcosis is dependent on the hydrophobicity of the substance with biochemical activation or reaction involved. Such narcotic effects are also referred to as minimum or base-line toxicity. Polar narcotics such as the category phenols are usually characterised by having hydrogen bond donor acidity and are thought to act by a similar mechanism to the inert, narcotic compounds but to exhibit above base-line toxicity.

Values for different toxicity endpoints have been calculated using the software program ECOSAR⁵, which comprises quantitative structure-activity relationships (QSARs), developed for calculating aquatic toxicity (Table 3). As expected for polar narcotic substances the aquatic toxicities of the category phenols increase in line with their log Kow. These calculated results are broadly supported by the available experimental data.

Mammalian toxicity

It is reasonable to consider the mutagenic potential of all the category phenols together since the only functional group is the phenolic, which is not a structural alert for mutagenicity. The data supports this as there is a consistent absence of genotoxicity in both bacterial and mammalian tests.

The acute (single-dose) toxicity of these alkylphenols also shows consistency, with LD₅₀ values from about 1000 mg/kg to over 2000 mg/kg. This demonstrates a generally very low level of acute systemic toxicity, despite the general tendency for the chemicals to be, at least, irritants to skin.

A useful range of repeat-dose toxicity data is available for four of the category members. The studies range from 28-day and 90-day general toxicity studies, through developmental toxicity and reproductive/developmental screening, to recently conducted multigeneration reproductive studies. The dosage at which the relatively mild general toxicity appears tends only to fall below 100 mg/kg/day with extended treatment, and an overall NOAEL for the category is indicated to be in the region of 20 mg/kg/day. There was no evidence of an effect on reproductive function at dosages up to 150 mg/kg. One reproductive screening study reported increased 'breeding loss' and also reduced pup weight gain and survival in early lactation at 750 mg/kg, effects that might have been secondary to 'severe toxic symptoms' reported in the dams at this dosage. There was no effect on development, other than indications of a very mildly oestrogenic effect of *p*-nonylphenol at a high dose level (200-300 mg/kg/day) in a multigeneration study. For *p*-*tert*-butylphenol, long-term treatment with high dietary dose levels caused hyperplastic changes in the forestomach epithelium of rats and hamsters, a likely consequence of the irritancy of the material. The relevance of this for human hazard is doubtful, particularly as there is no analogous structure in humans to the forestomach of rodents.

The mammalian toxicity data is summarised in Table 4.

⁴ Verhaar, H.J.M. van Leeuwen, C.J. and Hermens, J.L.M., *Classifying Environmental Pollutants. 1: Structure-Activity Relationships for Prediction of Aquatic Toxicity*, Chemosphere (25), pp 471 – 491 (1992).

⁵ ECOWIN v.0.99e. ECOSAR Classes for MicroSoft Windows, United States Environmental Protection Agency.

TABLE 1 - Physical Chemistry Properties of Alkylphenols

Phenol	CAS No.	MW	M.Pt. (°C)		B.Pt. (°C)		V.P. (Pa)		Log Kow		Water Sol. (mg/l)	
			Calc.	Exptl.	Calc.	Exptl.	Calc.	Exptl.	Calc.	Exptl.	Calc.	Exptl.
2,3,6-Trimethylphenol	2416-94-6	136	41	65	230	222	3.31	<10	3.15	2.72	668	1420
<i>p</i> -tert-Butylphenol	98-54-4	150	37	100	230	237	3.57	0.5	3.42	3.31	344	800
<i>o</i> -sec-Butylphenol	89-72-5	150	39	14	237	224	2.31		3.46	3.27 ¹	319	
2-tert-Butylphenol	88-18-6	150	37	-7	230	223	3.57	12	3.42	3.31	344	
<i>p</i> -tert-Amylphenol	80-46-6	164	48	95	248	263	1.04		3.91	4.03	113	168
Heptyl derivs (<i>p</i> -heptylphenol)	72624-02-3	192	73		296		0.037		5.01		9.65	
<i>p</i> -tert-Octylphenol	140-66-9	206	73	81	281	282	0.091	0.21	5.28	4.12	4.82	18
<i>p</i> -Octylphenol	1806-26-4	206	83		311	296	0.013		5.50		3.11	
2,4-Di- <i>tert</i> -butylphenol	96-76-4	206	77	57	281	264	0.082	1.0	5.33		4.32	12
2,6-Di- <i>tert</i> -butylphenol	128-39-2	206	77	37	281	253	0.082	1.01	4.48	4.5	23.0	4.11
<i>p</i> -(<i>alpha</i> , <i>alpha</i> -Dimethylbenzyl)phenol	599-64-4	212	103	72	328	335	0.0030		4.12		43.3	
<i>p</i> -Nonylphenol	84852-15-3	220	90	25	316	310	0.0080	0.0046	5.92	3.28	1.16	3.93 ²
2,4-Di- <i>tert</i> -pentylphenol	120-95-6	234	89	26	311		0.011		6.31		0.444	
<i>p</i> -Dodecylphenol	210555-94-5	262	102		330	308	0.0028		7.17		0.058	
4-sec-Butyl-2,6-di- <i>tert</i> -butylphenol	17540-75-9	262	102	47	330	275	0.0028		6.43		0.248	
2,4,6-Tri- <i>tert</i> -butylphenol	732-26-3	262	104	131	325	278	0.0035	0.088	6.39	6.06	0.267	
2,4-Bis(<i>alpha</i> , <i>alpha</i> -dimethylbenzyl)phenol	2772-45-4	330	172	65	436	>300	7.8E-07		6.73		0.055	

The following programs were used for calculations:

Melting point, boiling point & vapor pressure: MPBWIN v1.30

The above programs were run using the interface program EPIWIN v3

Water solubility: WSKOW v1.33

Log Kow: KOWWIN v1.63

Numbers have been rounded and the mid-point reported for ranges.

Calculated results have been included in the robust summaries only when no experimental result was available. All calculations were performed specifically for this HPV submission.

All water solubility calculations were performed using log Kow values obtained using the program KOWWIN v1.63.

¹ Value from KOWWIN database

² Seawater

TABLE 2 - Level I Fugacity Modelling Results for Alkylphenols

Phenol	CAS No.	MW	Air	Soil		Water		Sus. Sed.		Fish		Sediment	
				%	%	%	%	%	%	%	%	%	%
2,3,6-Trimethylphenol	2416-94-6	136	11.6	27.9	59.9	0.019	0.016						0.62
<i>p</i> -tert-Butylphenol	98-54-4	150	0.66	63.0	34.9	0.044	0.0036						1.40
<i>o</i> -sec-Butylphenol	89-72-5	150	7.54	56.7	34.4	0.039	0.0032						1.26
2-tert-Butylphenol	88-18-6	150	27.0	46.3	25.6	0.032	0.0026						1.03
<i>p</i> -tert-Amylphenol	80-46-6	164	1.88	87.0	9.16	0.060	0.0049						1.93
Heptyl derivs (p-heptylphenol)	72624-02-3	192	0.16	96.6	1.07	0.067	0.0055						2.15
<i>p</i> -tert-Octylphenol	140-66-9	206	3.61	86.9	7.45	0.060	0.0049						1.93
<i>p</i> -Octylphenol	1806-26-4	206	0.060	97.4	0.35	0.068	0.0055						2.16
2,4-Di-tert-butylphenol	96-76-4	206	1.75	95.6	0.50	0.066	0.0054						2.12
2,6-Di-tert-butylphenol	128-39-2	206	25.6	70.3	2.51	0.049	0.0040						1.56
<i>p</i> -(alpha, alpha-Dimethylbenzyl)phenol	599-64-4	212	0.023	90.2	7.72	0.063	0.0051						2.00
<i>p</i> -Nonylphenol	84852-15-3	220	1.87	60.7	36.0	0.042	0.0034						1.35
2,4-Di-tert-pentylphenol	120-95-6	234	0.063	97.6	0.034	0.068	0.0055						2.17
<i>p</i> -Dodecylphenol	210555-94-5	262	0.019	97.7	0.0075	0.068	0.0055						2.17
4-sec-Butyl-2,6-di-tert-butylphenol	17540-75-9	262	0.0245	97.7	0.041	0.068	0.0055						2.17
2,4,6-Tri-tert-butylphenol	732-26-3	262	1.65	96.1	0.095	0.067	0.0054						2.13
2,4-Bis(alpha, alpha-dimethylbenzyl)phenol	2772-45-4	330	1.95E-05	97.7	0.021	0.068	0.0055						2.17

TABLE 3 - Summary of Acute Aquatic Toxicity Data for Alkylphenols

Phenol	CAS No.	MW	Calc. log Kow	Fish (96h LC50)		Daphnid (48h EC50)		Algae (96h EC50)	
				Calc.	Exptl.	Calc.	Exptl.	Calc.	Exptl.
2,3,6-Trimethylphenol	2416-94-6	136	3.15	3.9	16	2.5	12.6 ¹	6.4	19 ²
<i>p</i> -tert-Butylphenol	98-54-4	150	3.42	2.9	5.14	2.1	3.9	4.1	
<i>o</i> -sec-Butylphenol	89-72-5	150	3.46	2.8		2.0		3.8	
2-tert-Butylphenol	88-18-6	150	3.42	2.9	15.5 ³	2.1		4.1	
<i>p</i> -tert-Amylphenol	80-46-6	164	3.91	1.6		1.5		1.7	
Heptyl derivs (p-heptylphenol)	72624-02-3	192	5.01	0.40	0.85	0.61		0.21	2.5
<i>p</i> -tert-Octylphenol	140-66-9	206	5.28	0.29	0.25	0.51	0.27	0.13	1.9
<i>p</i> -Octylphenol	1806-26-4	206	5.50	0.21		0.41		0.082	
2,4-Di- <i>tert</i> -butylphenol	96-76-4	206	5.33	0.27		0.48		0.12	
2,6-Di- <i>tert</i> -butylphenol	128-39-2	206	4.48	0.90	7.6	1.1	1.7 ¹	0.65	1.2
<i>p</i> -(alpha, alpha-Dimethylbenzyl)phenol	599-64-4	212	4.12	1.5		1.6		1.4	
<i>p</i> -Nonylphenol	84852-15-3	220	5.92	0.13	0.31	0.30	0.14	0.037	0.41
2,4-Di- <i>tert</i> -pentylphenol	120-95-6	234	6.31	0.076		0.22		0.018	
<i>p</i> -Dodecylphenol	210555-94-5	262	7.17	0.025		0.11		0.003	
4-sec-Butyl-2,6-di- <i>tert</i> -butylphenol	17540-75-9	262	6.43	0.072		0.22		0.016	
2,4,6-Tr- <i>tert</i> -butylphenol	732-26-3	262	6.39	0.076		0.226		0.017	
2,4-Bis(alpha, alpha-dimethylbenzyl)phenol	2772-45-4	330	6.73	0.059		0.21		0.011	

Toxicities were calculated by the program ECOSAR v0.99e using log Kow values estimated by KOWWIN v1.63. Both programs were run using the interface program EPIWIN v3.

¹ 24h

² 72h

³ Result from a study that used a formulation of 2-*tert*-butylphenol.

TABLE 4 - Available Data on Mammalian Toxicity of Alkylphenols

CAS No.	2416-94-6	98-54-4	89-72-5	88-18-6	80-46-6	72624-02-3	140-86-9	1806-26-4	96-76-4
Acute Toxicity (oral, mg/kg)	>2000	>2000	>200, <2000	789 oral, rat	1830	>200, <2000	>2000	1200	1500
Irritancy, skin (eye)	-	Irritant	Corrosive	Corrosive	Corrosive	Irritant (Irritant)	Mild irritant (Irritant)	-	Irritant
Genetic Toxicity	Neg	Neg*	Neg	Neg	Neg	Neg	Neg	-	-
Repeated-dose toxicity	-	Hamster 20 week, Rat 1 year: EL 15000 ppm	-	-	-	-	Rat 90d: NOAEL 30 ppm EL 300 ppm	-	-
Reproductive toxicity	-	-	-	-	-	-	Rat 2gen: NOAEL 200 ppm (systemic tox.), 2000 ppm (repro. tox.) EL 2000 ppm	-	-
Developmental toxicity	-	-	-	-	-	-	-	-	-

* Gene mutation assay using mouse lymphoma showed no evidence of mutagenic response after 3 hrs (normal exposure time) but a positive response at 24 hrs.
 EL = Effect level MatEL = Maternal effect level NOAEL = No-adverse effect level Dv = Developmental Mat = maternal Neg = Negative
 - = No data available

TABLE 4 - Available Data on Mammalian Toxicity of Alkylphenols (continued)

CAS No.	128-39-2	599-64-4	84852-15-3	120-95-6	210555-94-5	17540-75-9	732-26-3	2772-45-4
Acute Toxicity (oral, mg/kg)	>5000	1770	1882	920	-	4800	1670 (males) 1610 (females)	-
Irritancy, skin (eye)	Irritant	-	Corrosive (Irritant)		-	-		-
Genetic Toxicity	Neg	Neg	Neg	-	-	-	-	-
Repeated-dose toxicity	Rat 28d: NOAEL 15 mg/kg/d EL 100 mg/kg/d	-	Rat 28d: NOAEL 100 mg/kg/d EL 400 mg/kg/d Rat 90d: NOAEL 50 mg/kg/d EL 150 mg/kg/d	-	-	-	Rat 24 months: NOAEL 30 ppm Dogs 11 days: increased liver metabolism above 50 mg/kg/d + some autonomic signs at 450 mg/kg/d.	-
Reproductive toxicity		-	Rat 3gen: NOAEL (systemic & repro tox.) 200 ppm ca 20 mg/kg/d EL (repro tox.) 650 ppm ca 50 mg/kg/d	-	-	-		-
Developmental toxicity	Rat 421: NOAEL 150 mg/kg/d MatEL 750 mg/kg/d	-	Rat: MatNOAEL 75 mg/kg/d DvNOAEL 300 mg/kg MatEL 300 mg/kg/d	-	-	-		-

EL = Effect level
Negative

- = No data available

MatEL = Maternal effect level

NOAEL = No-adverse effect level

Dv = Developmental

Mat = maternal

Neg =

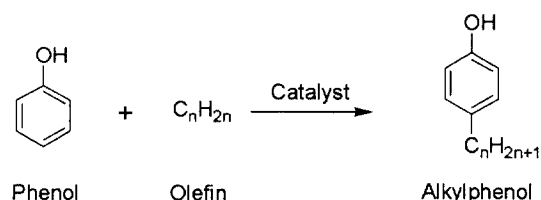
INDUSTRIAL MANUFACTURING AND COMMERCIAL APPLICATIONS OF ALKYLPHENOLS

para-Substituted alkylphenols

The *para*-substituted alkylphenols are typically made from an olefin and phenol using an acid catalyst (Figure 1). The side chains tend to be highly branched with predominately a tertiary carbon attached to the phenol ring. In some cases, a small amount of *ortho* isomer is co-produced and must be removed in a purification step.

The olefins are either a relatively pure, low molecular weight material with an α -olefin structure such as for PTBP, PTAP, and PTOP or a mixture of isomeric olefins as for PHP, POP, PNP and PDDP. (See Table 5).

Figure 1 - Synthesis of *para*-substituted alkylphenols

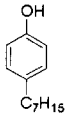
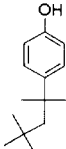
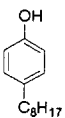
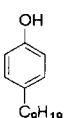
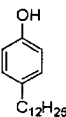


The manufacturing processes for the various *para*-substituted alkylphenols, are conducted in fully automated, closed systems that have been engineered to comply with applicable environmental laws and regulations. In the typical reaction, a fixed bed reactor containing a solid acid catalyst is fed with phenol and olefin at the appropriate ratio to produce a mixture of *ortho*- and *para*-alkylphenol and a small amount of by-products. The product is recovered at the required quality by fractional vacuum distillation.

Table 5 – Structure, manufacture and commercial applications of *para*-substituted alkylphenols

Compound	Name	CAS NO.	Starting Olefin	Structure	Applications
PTBP	<i>p</i> - <i>tert</i> -Butylphenol	98-54-4	Isobutylene		Phosphate esters, fragrances, oil field chemicals, demulsifiers, polycarbonate chain terminator, glycidyl ethers
PTAP	<i>p</i> - <i>tert</i> -Amylphenol	80-46-6	Isoamylene		Demulsifiers, biocides, fragrances

Table 5 (continued)

Compound	Name	CAS NO.	Starting Olefin	Structure	Applications
PHP	Heptyl derivs (<i>p</i> -Heptylphenol)	72624-02-3	Heptylene		Oil additive intermediate, phenolic resins
PTOP	<i>p</i> -tert-Octylphenol	140-66-9	Diisobutylene		Surfactants, tackifier resins, ink resins, polycarbonate chain terminator, ultraviolet stabilizers
POP	<i>p</i> -Octylphenol	1806-26-4	Octene		Surfactants, phenolic resins
PNP	<i>p</i> -Nonylphenol	84852-15-3	Nonene		Demulsifiers, antioxidant intermediate, surfactants, epoxy resin hardener, heat stabilizer for PVC, phenolic resins
PDDP	<i>p</i> -Dodecylphenol	210555-94-2	Dodecene		Surfactants, lube oil additives, intermediate, phenolic resins

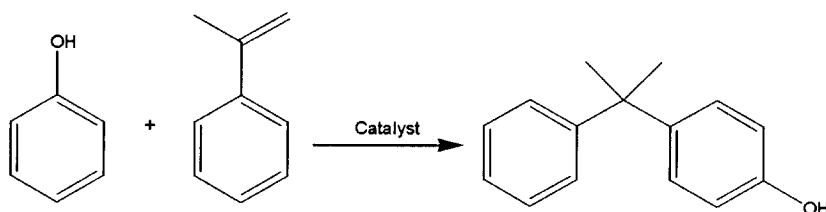
Alkylphenols tend to darken on contact with iron and oxygen. These materials must be stored and shipped in stainless steel vessels under an inert atmosphere. Contact with carbon steel should be avoided.

The commercial uses of the *para*-substituted alkylphenols are numerous and many are listed in Table 5. Typical applications include the use of the alkylphenols as intermediates in the synthesis of primary and secondary antioxidants, demulsifiers, surfactants, lube oil additives, biocides, fragrances, and various types of tackifier, ink and phenolic resins. They also find use as polymerization inhibitors, epoxy resin hardeners, heat stabilizers, and polycarbonate chain terminators.

***p*-(*alpha*, *alpha*-Dimethylbenzyl)phenol (4-cumylphenol)**

The manufacturing process for 4-cumylphenol [PCP, *para*-cumylphenol, *p*-(*alpha*, *alpha*-dimethylbenzyl)phenol4-(1-methyl-1-phenylethyl)phenol], CAS RN = 599-64-4, is conducted in a fully automated, closed system that has been engineered to comply with applicable environmental regulations. An appropriate blend of phenol and 2-methylstyrene [α -methylstyrene, AMS] is passed through a fixed-bed of a solid acid catalyst. The crude alkylphenol stream containing phenol, cumylphenol isomers and reaction byproducts is rectified by vacuum fractional distillation to achieve the required purity for PCP. The process is depicted by the chemical equation in Figure 2.

Figure 2 – Synthesis of PCP

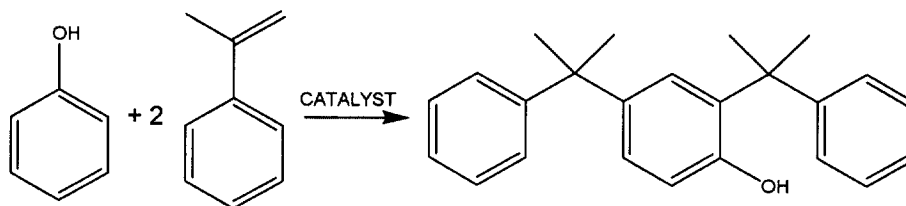


PCP exhibits physical characteristics and chemical characteristics similar to those of other para-alkylated phenols. PCP is used as a chemical intermediate in the synthesis of specialty surfactants and phenolic resins. Its primary use is as a chain-stopper in polycarbonate resins to control molecular weight and physical properties.

2,4- Bis(*alpha*, *alpha*- dimethylbenzyl)phenol (2,4-dicumylphenol)

The manufacturing process for 2,4-dicumylphenol [2,4-DCP; 2,4-*bis*(1-methyl-1-phenethyl)phenol], CAS RN = 2772-45-4, is conducted in a processing unit that has been engineered to comply with applicable environmental regulations. α -Methylstyrene (AMS) is added into a reactor containing phenol and an acidic catalyst at a controlled rate. Once the reactor contents have reached the desired composition, the catalyst is separated from the crude alkylate. This material, containing mono-cumylphenol isomers, DCP and byproducts is rectified by fractional vacuum distillation to achieve the desired purity. The process is shown in Figure 3.

Figure 3 – Synthesis of 2,4-DCP

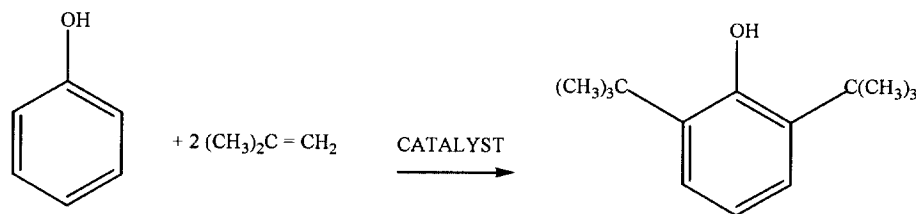


The predominant use 2,4-DCP is as a chemical intermediate. In its primary use, 2,4-DCP is converted to a benzotriazole to produce a UV stabilizer. It can also be used as a primary antioxidant or can be converted to a secondary antioxidant as a phosphite. In each case, the material is used in high temperature polymers where higher thermal stability is needed during high temperature molding processes.

2,6-Di-*tert*-butylphenol

The manufacturing process for 2,6-di-*tert*-butylphenol (2,6-DTBP), CAS RN = 128-39-2, is conducted in a fully automated, closed system that has been engineered to comply with applicable environmental regulations. An autoclave reactor is first charged with phenol and catalyst. Then isobutylene is added into the reaction under controlled conditions to generate a crude alkylate. The catalyst is separated from this alkylate. The product is recovered at the quality required by fractional vacuum distillation. See Figure 4.

Figure 4 – Synthesis of 2,6-DTBP



Like other alkylphenols, 2,6-DTBP is susceptible to discoloration in air. This is the result of an oxidation reaction with oxygen. The presence of two ortho-*tert*-butyl groups stabilizes the phenoxy radical generated by oxidation. This stabilizing influence also explains the good antioxidant property of 2,6-DTBP.

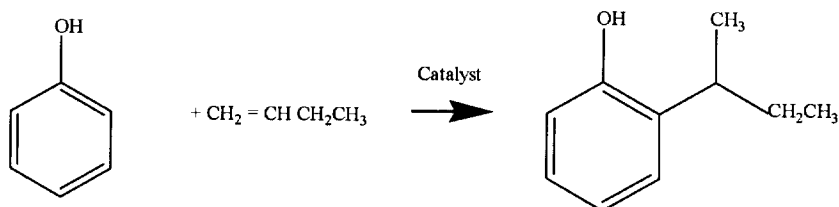
2,6-DTBP can be used as an antioxidant, and it is an important commercial building block for hindered phenolic antioxidants. In these applications, reactions are carried out at the 4-position of 2,6-DTBP to impart a desirable characteristic, such as solubility or reduced volatility, to the antioxidant. 2,6-DTBP can be utilized as a starting material in the synthesis of 4,4'-biphenol. Two molecules of 2,6-DTBP are oxidatively coupled under appropriate conditions to the tetra-substituted biphenol. The butyl groups are subsequently cleaved from the ring to generate the biphenol.

o-*sec*-Butylphenol (2-*sec*-butylphenol)

2-*sec*-Butylphenol (OSBP) CAS RN = 89-72-5, can be produced by two different processes. Both processes have been engineered to comply with applicable environmental regulations using fully automated, closed systems. The choice of process is based on business considerations.

In the first process, a mixture of 1-butene and phenol is passed through a fixed bed of ion exchange resin. The crude alkylphenol, containing phenol, sec-butylphenol isomers and other alkylates is rectified by vacuum fractional distillation. In the other process, 1-butene is metered into a solution of a homogeneous catalyst in phenol. Again the crude alkylphenol is rectified by fractional vacuum distillation to achieve the required OSBP purity. Both processes are depicted by the chemical equation in Figure 5.

Figure 5 – Synthesis of OSBP

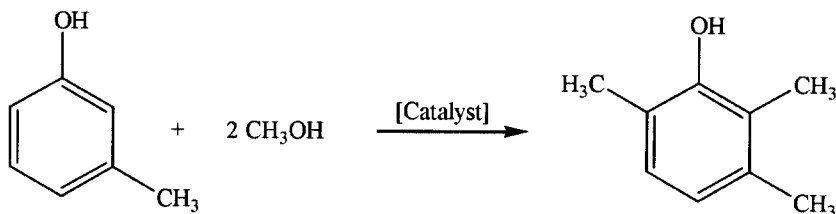


OSBP is mainly used as a chemical intermediate in the synthesis of insecticides, herbicides and as a polymerization inhibitor. It undergoes reactions on the aromatic ring and the phenolic hydroxyl group. It is somewhat less acidic than phenol.

2,3,6-Trimethylphenol

The manufacturing process for 2,3,6-trimethylphenol (TMP), CAS RN = 2416-94-6, is conducted in an automated, closed system that has been engineered to comply with applicable environmental regulations. A fixed bed reactor containing a mixed metal oxide catalyst is fed with a mixture of methanol and 3-methylphenol. The product is separated from the byproduct, water, then distilled under fractional vacuum distillation to achieve the quality required. See Figure 6.

Figure 6 – Synthesis of 2,3,6-TMP



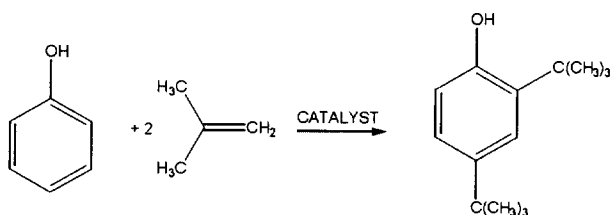
2,3,6-TMP is an intermediate in synthetic Vitamin E, in antioxidants and in polymer applications. Each application involves the susceptibility of the phenolic ring to oxidation. Under normal storage conditions, 2,3,6-TMP is blanketed with an inert gas to mitigate the reaction between atmospheric O_2 and 2,3,6-TMP.

2,3,6-TMP also displays another characteristic of phenols. It has a weakly acidic proton which can react with bases.

2,4-Di-*tert*-butylphenol

The manufacturing process for 2,4-di-*tertiary*-butylphenol (2,4-DTBP), CAS RN = 96-76-4, is conducted in a fully automated, closed system that has been engineered to comply with applicable environmental regulations. A reactor is first charged with phenol and an acid catalyst. Then isobutylene is added into the reaction under controlled conditions to generate a crude alkylate. The crude alkylate contains 2,4-DTBP, mono- and tri-butylphenol, some isomers and by-products. The catalyst is separated from this alkylate. The product is recovered at the required quality by fractional vacuum distillation. The chemical equation for the process is shown in Figure 7.

Figure 7 – Synthesis of 2,4-DTBP

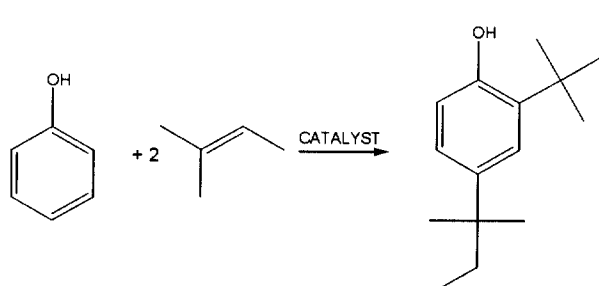


The primary use of 2,4-DTBP is in the synthesis of triaryl phosphites. These are used as secondary antioxidants, primarily in plastics. 2,4-DTBP also can be used to produce primary phenolic antioxidants by condensing it with an aldehyde at the ortho position to produce a high molecular weight bisphenolic, which stabilizes polyolefins, styrenics and natural or synthetic rubber. 2,4-DTPB can also be converted benzotriazole derivatives or an ester of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, both of which are used as UV stabilizers.

2,4-Di-*tert*-pentylphenol (2,4-Di-*tert*-amylphenol)

The process for manufacturing 2,4-di-*tertiary*-amylphenol [2,4-DTAP; 2,4-bis(1,1-dimethylpropyl)phenol], CAS RN = 120-95-6, is conducted in a fully automated, closed system that has been engineered to comply with applicable environmental regulations. First, a reactor is charged with phenol and an acidic catalyst. Then isoamylene (a 90/10 mixture of 2-methyl-2-butene and 2-methyl-1-butene) is added into the reaction under controlled conditions to generate a crude alkylate. The crude alkylate contains 2,4-DTAP, mono- and tri-amylphenol, some isomers and by-products. The catalyst is separated from this alkylate. The product is recovered at the required quality by fractional vacuum distillation. The chemical equation for the process is shown in Figure 8.

Figure 8 – Synthesis of 2,4-DTAP

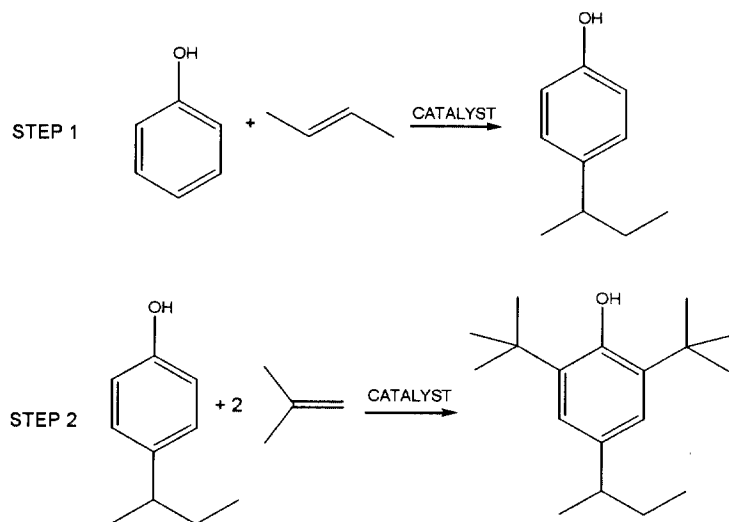


The major use of 2,4-DTBP is in the production of UV stabilizers. The major one is a benzotriazole-based UV absorber used in polyolefin films, outdoor furniture and automotive clear coat finishes. A number of phenoxyacetic acid derivatives are used in the photographic industry. Reaction with ethylene oxide produces a speciality surfactant that can be used to treat cotton fibres. A similar product can be used as a fuel additive acting as a corrosion inhibitor.

4-sec-Butyl-2,6-di-tert-butylphenol (ISONOX® 132)

The process for manufacturing ISONOX® 132 [2,6-di-tert-butyl-4-sec-butylphenol], CAS RN = 17540-75-9, is a two-step process that is conducted in fully automated, closed systems that have been engineered to comply with applicable environmental regulations. In the first step, a fixed bed reactor containing a solid acid catalyst is charged with phenol and 2-butene to produce a mixture of ortho- and *para*-sec-butylphenol (OSBP & PSBP). This mixture is rectified by distillation. In the second step, the purified PSBP, isobutylene, and an appropriate catalyst are added in a reactor under controlled conditions to generate a crude alkylate. The crude alkylate is separated from the catalyst. The product is recovered at the required quality by fractional vacuum distillation. The chemical equation for the process is shown in Figure 9.

Figure 9 – Synthesis of ISONOX® 132

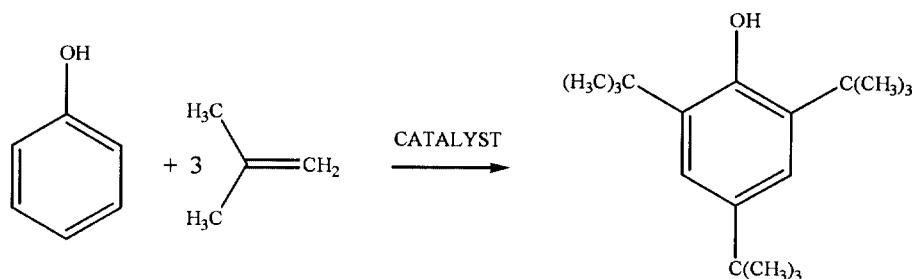


The primary use of ISONOX® 132 is as an antioxidant. It is a low cost, highly active liquid stabilizer for polyols, PVC, polyurethane, adhesives and functional fluids. ISONOX® 132 has received FDA approval for use as an antioxidant in indirect food contact applications in plasticized vinyl chloride homo- and copolymers (PVC).

2,4,6-Tri-*tert*-butylphenol

The manufacturing process for 2,4,6-tri-*tert*-butylphenol (2,4,6-TTBP), CAS RN = 732-26-3, is conducted in a fully automated, closed system that has been engineered to comply with applicable environmental regulations. An autoclave reactor is first charged with phenol and catalyst. Then isobutylene is added into the reaction under controlled conditions to generate a crude alkylate. The catalyst is separated from this alkylate. The product is recovered at the quality required by either fractional vacuum distillation or recrystallization in an appropriate solvent.

Figure 10 – Synthesis of 2,4,6-TTBP

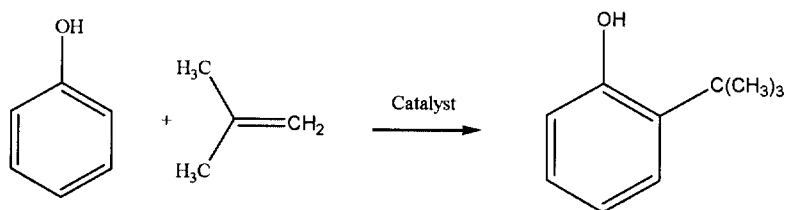


Like most alkylphenols with bulky substituents, 2,4,6-DTBP can be used as a primary antioxidant or as an intermediate in the synthesis of primary antioxidants. Its primary commercial use, however, is an intermediate in the synthesis of polymer stabilizers that provide enhanced hydrolytic, thermal oxidative, and UV stability to thermoplastic resins.

2-*tert*-Butylphenol

The manufacturing process for 2-*tert*-butylphenol (*ortho*-*tertiary* butylphenol, OTBP), CAS RN = 88-18-6, has been engineered to comply with applicable environmental regulations using a fully automated, closed system. Phenol and an appropriate *ortho*-alkylating catalyst are charged to a reactor followed by the controlled addition of isobutylene to generate a crude alkylate. See Figure 11. When the reaction is complete, the catalyst is removed from the mixture and the product is recovered at the required quality by fractional vacuum distillation.

Figure 11 – Synthesis of OTBP



OTBP is used as a starting material for the synthesis of flavor and fragrance chemicals, antioxidants, insecticides, and phenolic resins. Compounds for the fragrance industry can be made from *cis*-2-*tert*-butylcyclohexanol [7214-18-8] that is obtained by hydrogenation of OTBP in the presence of Pd/Al₂O₃ or Ru/Al₂O₃ catalysts.

ALKYLPHENOL CATEGORY TEST PLANS

CAS No.	2416-94-6	98-54-4	89-72-5	88-18-6	80-46-6	72624-02-3	140-66-9	1806-26-4	96-76-4	128-39-2	599-64-4	84852-15-3	120-95-6	210555-94-5	17540-75-9	732-26-3	2772-45-4
Physical Chemistry Properties																	
Melting point	D	D	D	D	D	C	D	C	D	D	D	D	D	C	D	D	D
Boiling point	D	D	D	D	D	C	D	D	D	D	D	D	C	D	D	D	D
Vapour pressure	D	D	C	D	C	C	D	C	D	D	C	D	C	C	C	D	C
Log Kow	D	D	C	D	D	C	D	C	C	D	C	D	C	C	C	D	C
Water solubility	D	D	C	C	D	C	D	C	D	D	C	D	C	C	C	C	C

Key: C= endpoints fulfilled using calculated data
D= endpoints fulfilled using adequate existing experimental data

ALKYLPHENOL CATEGORY TEST PLANS (continued)

CAS No.	2416-94-6	98-54-4	89-72-5	88-18-6	80-46-6	72624-02-3	140-66-9	1806-26-4	96-76-4	128-39-2	599-64-4	84852-15-3	120-95-6	210555-94-5	17540-75-9	732-26-3	2772-45-4
Environmental Fate and Pathway																	
Photodegradation	C	C	C	C	C	C	C	C	C	C/D	C	C	C	C	C	C	C
Stability in water	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Transport/ Distribution- fugacity model	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Biodegradation	D	D	S	S	S	S	D	S	D	D	S	D	S	S	S	S	S
Ecotoxicology																	
Acute Fish	C/D	C/D	C	C/D	C	C/D	C/D	C	C	C/D	C	C/D	C	C	C	C	C
Acute Algae	C/D	C	C	C	C	C/D	C/D	C	C	C/D	C	C/D	C	C	C	C	C
Acute Daphnia	C/D	C/D	C	C	C	C	C/D	C	C	C/D	C	C/D	C	C	C	C	C

Key: * = Although no studies on abiotic hydrolysis were found, no testing is proposed because the category phenols do not possess any functional groups that are regarded as being susceptible to hydrolysis under environmental conditions.

T = testing required (Level III Fugacity Model to be run)

C = endpoints fulfilled using calculated data

D = endpoints fulfilled using adequate existing experimental data

S = endpoints fulfilled using category approach (read across).

ALKYLPHENOL CATEGORY TEST PLANS (continued)

CAS No.	2416-94-6	98-54-4	89-72-5	88-18-6	80-46-6	72624-02-3	140-66-9	1806-26-4	96-76-4	128-39-2	599-64-4	84852-15-3	120-95-6	210555-94-5	17540-75-9	732-26-3	2772-45-4
TOXICOLOGY																	
Acute toxicity	D	D	D	D	S	D	D	D	D	D	D	D	D	S	D	D	S
Genetic toxicity- bacterial	D	D	D	D	D	D	D	S	S	D	D	D	S	S	S	S	S
Genetic toxicity- non bacterial- <i>in vitro</i>	S	S	S	S	S	S	S	S	S	D	S	D	S	S	S	S	S
Genetic toxicity- non bacterial- <i>in vitro</i>	S	T	S	S	S	S	S	S	S	D	S	D	S	S	S	S	S
Repeated Toxicity	S	D	S	S	S	S	D	S	S	D	S	D	S	S	S	D	S
Repro/ Developm. Toxicity	S	S	S	S	S	S	D	S	S	D	S	D	S	S	S	S	S

Key:

S= endpoints fulfilled using category approach (read across)

D= endpoints fulfilled using adequate existing experimental data

T = testing required